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Epidemiology of chronic non-specific lung disease (chronic bronchitis); a critical analysis of three surveys of CNSLD carried out in the Netherlands

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Summary, conclusions, and desiderata

SUMMARY

The present thesis describes and analyses the results of three field surveys of chronic non-specific lung disease (CNSLD). The surveys were conducted in three Dutch communities, namely Meppel, a small town without appreciable chemical or physical atmospheric pollution; Vlagtwedde, a rural municipality, where there is also no atmospheric pollution, and Vlaardingen, a town with considerable atmospheric pollution. The surveys were conducted on random samples of the male and female population aged 40 to 64 years.

Chapter I briefly discusses what is understood by epidemiology and what methods of investigation are used.

In Chapter II a number of field surveys conducted at home and abroad are reviewed. A description is given of the methods of investigation and the frequency of chronic respiratory disease found in these surveys. It appears that only few studies allow comparisons to be made. Probably, this partly explains why the reported prevalence of 'chronic respiratory disease' varies widely (Tables 1 to 5).

In Chapter III the literature on the relation of a number of possibly 'causal' factors to the prevalence of CNSLD is considered (for the definition of CNSLD see Chapter V). We have only mentioned a few basic papers, one or two summaries of relevant literature, and literature dealing with specific points. Only the literature on field surveys has been discussed somewhat more elaborately. The literature has been considered against the background of our hypothesis that in patients with CNSLD there usually is a constitutional hereditary basis for symptoms and signs, which basis leads to disturbances in the reaction pattern (endogenous factors). In the presence of exogenous irritants these reaction disturbances give rise to the symptoms and signs. It is assumed that the latter may be influenced by factors of a more random nature, which determines the final clinical manifestation (p. 20). This chapter also mentions the parameters we have chosen for measuring the various endogenous and exogenous factors which might play a rôle as 'causal' factors.

Chapter IV deals with the standardization and choice of the methods by which the parameters of these 'causal' factors were quantified. The chapter also describes the choice and standardization of the methods of assessing what we assume to be the effect of the interaction of endogenous and exogenous factors (the symptoms and signs).

In Chapter V the definitions of CNSLD and CARA (abbreviation of Dutch term for chronic non-specific lung disease) are discussed. The persons found to have one or more of the following standardized respiratory symptoms have been regarded as CARA-positive: persistent cough, persistent phlegm, dyspnoea, wheeze, asthmatic attacks. Depending on the grades of dyspnoea and wheeze we have introduced two grades of CARA (p. 85).

The above definition of CARA is slightly different from Fletcher's definition of CNSLD (FLETCHER, 1961). However, the individual symptoms are still comparable. The reasons for our using this CARA definition are given on page 47.

In the present thesis we have used the term CNSLD when generally referring to the group of diseases usually named asthma, bronchitis, or emphysema. If we refer exclusively to a group characterized by the presence of sharply defined symptoms, the term CARA is used.

In Chapter VI a description is given of the object and the techniques of the investigation.

The objects envisaged were:

- a. Obtaining data on the prevalence of respiratory symptoms and signs in the Dutch population and gaining an insight into the natural history of CNSLD.
- b. Obtaining data on the relation of a number of postulated 'causal' factors to the symptoms and signs, which is of both fundamental and practical importance.
- c. Obtaining information on the correlation between the symptoms and the results of the objective investigation, partly with a view to possible future 'mass-screening' tests.

Furthermore, a description is given in this chapter of the techniques by which a number of subjective and objective data were collected. For the interview use was made of a shortened version of the standardized MRC-ECCS questionnaire. Questionnaires were completed on all the subjects, namely 2.065 men at Meppel, 1.084 men and 1.059 women at Vlagtwedde, and 649 men and 545 women at Vlaardingen. Moreover, a physical examination of the lungs was carried out and an X-ray was taken of these subjects. Different proportions of the persons interviewed were subjected to the following tests: counting the eosinophilic cells in the blood; cutaneous and intracutaneous allergy tests; helium wash-out test (not at Meppel); spirometry; histamine threshold test; macroscopic and microscopic sputum examination. With the exception of the helium wash-out test at Vlagtwedde – which was conducted on 360 subjects – and the histamine threshold test – which was conducted in all three communities on about 250 subjects – these tests were carried out at Meppel on about 75 per cent, at Vlagtwedde on about 50 per cent, and at Vlaardingen on approximately

100 per cent of the subjects interviewed. The concentration of so_2 and smoke particles in the atmosphere was measured extensively at Vlaardingen and on a small scale at Vlagtwedde (see p. 53). Also, in the two communities brief measurements were made of fungus spores and pollen in the air (see p. 53ff.).

Chapter VII discusses the representativeness of the samples, the reliability of the methods, and the question to what extent the prevalence of symptoms and signs and the comparison of the data between the various communities may have been influenced by disturbing factors (Tables 6 to 16).

In Chapter VIII the results of the subjective and objective investigations are described and analysed. These results are listed in Tables 17 to 120 and also in the text in a number of summarizing tables, the 'text tables'. With the aid of multiple regression analysis an attempt was made to find the relation between a number of individual factors (int. al. anthropometric data and respiratory symptoms) and reduction in VC or $\text{FEV}_{1.0}$.

In Chapter IX the findings are discussed. Consideration is given to the value of the findings in subjective and objective investigations, followed by a discussion of the prevalence of respiratory symptoms and signs in our surveys and their implication. In this connection attention is paid to the concepts of 'normal' and 'diseased'. Then follows a consideration of the relation between the results of the subjective and objective investigations and a few postulated 'causal' factors. Finally, the data of our investigation are compared with those of a number of comparable investigations carried out at home and abroad.

CONCLUSIONS

Considering the results, we come to the following conclusions:

1. In the three populations investigated the prevalence of symptoms and signs in the men and women in the age group 40 to 64 is high, but lower than generally found abroad. This prevalence is listed in the table opposite (Text table 16). Converted into a workable form, these figures reveal that of all these men and women about 30 per cent must be considered to have some degree of CNSLD (i.e. CARA). About 8 per cent are affected to such a degree that, in our opinion, regular treatment is required, and 1 to 2 per cent are badly handicapped.
2. Persistent cough and phlegm production (productive cough) on the one hand, and airways obstruction (as evident from symptoms as well as reduced $\text{FEV}_{1.0}$) on the other, are differently related to the postulated 'causal' factors. It looks as if 'productive cough' is mainly stimulated by 'exogenous' factors (pp. 121 to 126) whereas these factors seem to have little effect on the airways obstruction. The relation to one or more age-dependent factors is greater for airways obstruction than for 'productive cough' (p. 117 ff.).
3. This relation of the airways obstruction to age is not exclusively governed by 'exogenous' factors, but presumably also by 'endogenous' factors (p. 34), as also appears from our results (p. 118).

Text table 16

PREVALENCE OF RESPIRATORY SYMPTOMS AND PRESENCE OF 'ABNORMAL' FINDINGS IN OBJECTIVE INVESTIGATIONS, ACCORDING TO SEX AND AREA OF RESIDENCE

	MEN			WOMEN	
	MEPPEL %	VLAGTWEDDE %	VLAARDINGEN %	VLAGTWEDDE %	VLAARDINGEN %
Q. 5:					
Persistent cough	22.2	24.2	28.8	5.6	15.4
Q. 10:					
Persistent phlegm	15.9	15.6	26.0	3.8	11.0
Q. 14a:					
Dyspnoea gr. 2 or more	16.4	29.8	28.8	35.1	48.4
Q. 14b:					
Dyspnoea gr. 3 or more	5.8	8.6	6.6	9.6	19.8
Q. 15a:					
Ever wheezed	31.4	32.8	29.4	16.6	25.3
Q. 15c:					
Wheeze most days and/or nights	8.4	10.3	8.1	3.3	6.4
Q. 22 (16):					
Asthmatic attacks	4.4	5.1	2.1	3.7	3.4
Eosinophilia ($> 25 \times 11$)	—	VLAGTWEDDE: 13.3		VLAARDINGEN: 15.1	
Allergy (1 or more skin tests pos.)	—	23.5	49.6	29.2	51.5
Histamine threshold ≤ 32 mg/ml	—	74.5	63.8	70.9	65.4
FEV _{1.0} /vc per cent < 65	—	31.5	25.1	12.0	8.4
Slope of helium wash-out curve ≥ 4 %/sec.	—	25.2	20.9	23.3	15.3
Sputum handed in	63.0	42.4	47.8	19.9	21.4
Physical examination:					
Wheezing rhonchi	—	17.9	17.7	6.0	2.7
Râles	—	4.1	4.1	0.9	0.5
Prolongation of expiration	—	8.0	6.1	3.3	1.2
Radiographically labelled:					
'Anomalies of heart and/or bloodvessels'	—	30.4	11.4	33.5	12.1
'Emphysema'	—	11.6	3.0	3.1	1.2
'Bronchiectasis'	—	3.3	0.6	1.4	0.7

4. In the men more severe degrees of CARA are found than in the women, even on comparison of persons who have never smoked (p. 119). However, it may be that the influence of occupational factors partly accounts for this.

5. A higher prevalence of symptoms is found in persons with blood eosinophilia. This might point to a relation of CARA to allergy. Such a relation is not apparent from the results of the intracutaneous allergy tests. A few theories are discussed (p. 120).

6. In the group of persons with CARA there is a greater proportion with positive histamine threshold tests. It is not yet clear whether a positive histamine threshold test usually points to a really increased sensitivity of

the tissues relative to that of normal tissues, or whether it is usually only indicative of a changed initial condition of otherwise normally sensitive tissues, e.g. a constriction of the airways or a disturbed lung elasticity (p. 121).

7. There is a relation between smoking, particularly the smoking of cigarettes, and the prevalence of 'productive cough'. This symptom increases with smoking. There is only a small and not very distinct influence of smoking on the occurrence of airways obstruction (as evident from dyspnoea as well as spirometry) (p. 121 ff.).

8. There is a relation between living at Vlaardingen (urban factor) and the prevalence of persistent cough and phlegm. No relation is found between the urban factor and the presence of airways obstruction (p. 123 ff.).

9. The 'influence' of smoking on 'productive cough' is greater than that of the urban factor. A combination of the two factors has a considerably greater effect on cough and phlegm than either of the separate factors (p. 125).

10. The urban factor may be based on atmospheric pollution, but it is by no means impossible that other factors also play a rôle (p. 125).

11. In accordance with the results published by ASHFORD *et al.*, and several other investigators, and contrary to those of, int. al., TIFFENEAU *et al.*, we find that the $FEV_{1.0}/VC$ per cent ratio in persons without respiratory complaints show a decrease with increasing age (p. 136).

12. The information provided by the subjective investigation is on the whole in good agreement, but not entirely identical with that obtained by the objective investigation (p. 113). This difference in information, however, does not in our opinion point to either type of information being incorrect, but is indicative rather of the complementary nature of these methods of investigation (p. 109). An analysis of the correlation between the results of the spirometry, the helium wash-out test, and the peak flow measurements is still going on and the results will be published in due course.

13. The multiple regression analysis reveals that the presence of dyspnoea or blood eosinophilia is generally accompanied by a reduction of VC and $FEV_{1.0}$ which is greater than that found in the case of smoking.

14. The $FEV_{1.0}$ values (corrected for height and age) for non-smoking men without respiratory symptoms of the group of miners without pneumoconiosis investigated by ASHFORD *et al.* are only slightly lower than those of the men in our investigation (Text table 12). This might point to mine dust not giving rise to severe airways obstruction in men without respiratory symptoms. However, the somewhat greater difference in $FEV_{1.0}$ at the age of 40 might also be indicative of a selection factor.

15. The dependence on height and age of VC and $FEV_{1.0}$ in the CARA-negative groups is in good agreement with the formula of DE KROON *et al.* In the CARA-positive groups, however, there seems to be an additional age effect.

16. At Vlagtwedde a considerably smaller proportion of positive skin reactions is found than at Vlaardingen (both upon administering allergens and histamine

solutions). For this no explanation has been found. One might think of a reduced sensitivity of the skin of the inhabitants of Vlagtwedde as a result of a relatively greater exposure to all sorts of weather.

17. The proportion of sputa with micro-organisms is greater in the CARA-positive groups (about 20 per cent) than in the CARA-negative groups (about 10 per cent) (Table 114). The flora practically always consists of *Haemophilus influenzae* and/or *Micrococcus catarrhalis* and/or *Diplococcus pneumoniae*; occasionally it consists of Gram-negative rods. Only very seldomly is a streptococcus or staphylococcus found.

18. The roentgenological diagnosis of chronic respiratory disease, more particularly of 'emphysema', as accomplished in our investigation is altogether inadequate. In future investigations more emphasis should be laid on standardized criteria and methods.

19. Positive findings in the auscultation of the lungs are very frequently attended with presence of CARA as evident from the interview, but the reverse is not true. The relation of the auscultatory findings to the various symptoms is shown in Table 120.

DESIDERATA

Prior to the description and analysis of a great many data as obtained in our investigation, a choice should be made of the way in which these data are to be treated. When considering the results, it appears that either in collecting the data or in analysing them, particular items have inadvertently been left out which are needed in order to be sufficiently informed.

On the other hand, in the mailed questionnaires a number of questions were included which we did not want to use in the first place. But we did submit them because they might yet inform us about factors that could be of importance, be it for the interpretation of the present investigation or for the design of a future investigation.

The following is an enumeration of items which in our opinion still require working out. We are aware, however, that this list is not exhaustive.

1. *Items of the present investigation that are still to be analysed*

a. A multiple regression analysis using as the dependent variable the results of the helium wash-out test (in conformity with the analysis carried out for VC and $FEV_{1.0}$).

b. An investigation into the relation between the results of the spirometry, the helium wash-out test, and, as far as possible, the peak flow test. And also an investigation into the relation between the presence of abnormal helium curves and positive histamine threshold tests.

c. A comparison of the ways in which the prediction formulae of DE KROON *et al.*, M. CARA *et al.*, and TAMMELING fit to our data.

- d. A comparison between the inhabitants of Meppel, Vlagtwedde and Vlaardingen of the symptom prevalence in the light, moderate and heavy *cigarette* smokers.
- e. A comparison of the symptom prevalence and lung function values for men with and without a dusty occupation.
- f. A comparison of the symptom prevalence and the results of the lung function tests in various districts of Vlaardingen among which there might be a difference in the degree of air pollution.
- g. A comparison of the frequency distribution of VC and FEV_{1.0} values and of the results of the helium wash-out test for the men and women of Meppel, Vlagtwedde and Vlaardingen, classified, if possible, according to smoking habits, age and symptoms.
- h. An investigation into the relation between allergy and eosinophilia.
- i. A re-reading of the X-rays, use being made of standardized criteria (as far as applicable to our material).
- j. An investigation into the correlation of symptoms and signs to receiving treatment from a general practitioner or specialist.
- k. A study of the relation of symptoms and signs to 'allergic stigmata' (such as eczema and hay fever).
- l. An investigation into the relation of symptoms and signs to 'poor housing accommodation'.
- m. An investigation into the relation of symptoms and signs to positive answers to questions with regard to 'allergic relatives'. We realize, however, that the use for this purpose of a mailed questionnaire is subject to justified criticism.

2. *Items to be included in future investigations*

- a. Investigation of younger age groups.
- b. A further study of the reproducibility of symptoms and signs and a further investigation, mainly in the form of a follow-up study, of the meaning of finding such 'abnormalities'.
- c. Supplementation of the allergy test by means of dilution series.
- d. Supplementation of the histamine threshold test by investigating greater numbers and applying a further quantification.
- e. Large-scale measurements of weather conditions, and measurements of chemical, physical and biological air pollution.
- f. A further analysis of the influence of the occupation on people being affected by CNSLD.
- g. The additional use in the X-ray examination of (good!) lateral chest radiographs and of standardized criteria in reading the X-rays.
- h. Investigations of twins.